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(54) Title: ACTIVE SUBSTANCE CARRIER FOR RELEASING APOMORPHINE INTO THE BUCCAL CAVITY

(54) Bezeichnung: WIRKSTOFFTRÄGER FÜR DIE FREISETZUNG VON APOMORPHIN IN DER MUNDHÖHLE

(57) Abstract

The invention concerns a medicament preparation with a flat, foil-, paper- or wafer-like presentation for the application and release of active substances into the buccal cavity. The preparation is characterized in that it contains apomorphine or one of its therapeutically suitable salts.

(57) Zusammenfassung

Eine Arzneizubereitung mit flacher, folien-, papier- oder oblatenförmiger Darreichungsform zur Applikation und Freisetzung von Wirkstoffen in der Mundhöhle ist gekennzeichnet durch einen Gehalt an Apomorphin oder einem seiner therapeutisch geeigneten Salze.

A B S T R A C T

A pharmaceutical preparation having a flat, foil-shaped, paper-shaped or wafer-shaped administration form for application and release of active substances in the oral cavity is characterized by a content of apomorphine or one of its therapeutically acceptable salts.

Active substance carrier for the release of apomorphine in the oral cavity

The present invention relates to a pharmaceutical preparation for application of active substances in the region of the oral cavity or oral mucosa. In particular, it relates to a preparation which is adapted to be flat and in the form of a foil-, paper- or wafer-shaped administration form.

Flat active substance carriers have already been developed and produced, for various purposes. DE-OS 27 46 414 can be regarded as fundamental to this administration form, said document describing a foil-type tape of active substance, binder and further active substances, with a direct relation existing, by reason of the homogeneous thickness and density, between a unit of length of the tape and the dose of active substance contained therein. The advantages of the continuous dosage property have been recognized also by other applicants and have been described in specific individual variants. Thus, DE-PS 36 30 603 claims a flat-shaped carrier material, for example in the form of a separating layer, having an active substance-containing coating, the latter having to be peeled off the carrier material after having been previously separated into dosage units.

The practicality of the flat format in general as well as the advantages afforded by the production of this administration form and by the dosage employing said administration form have been recognized in the prior art. Further advantages can be derived such as the fact that, relative to the weight of the administration form, a relatively large surface may be printed on the said

administration form, thus increasing intake safety as well as affording the possibility of discrete intake without any liquid being available.

If an active substance is to be applied that can be brought to absorption via the oral mucosa, a flat, film- or paper-like active substance carrier enables a more rapid onset of action than in the case of application of conventional administration forms, such as tablets. Tablets are typically adapted for active substance release in the gastrointestinal tract after swallowing. Usual, rapidly disintegrating tablets release active substance in the stomach, with the disintegration of the administration form being a precondition for the active substance release. Frequently, the disintegration of a tablet in the liquids contained in the gastrointestinal tract is a multi-stage process. If the tablet has a coat, this must first disintegrate in order to expose the pressed piece. This is followed by so-called primary disintegration, during which the tablet disintegrates into small fragments, e.g. into the granules from which it was pressed, said fragments in turn disintegrating during the so-called secondary disintegration into the powders they are composed of. Whereas the primary disintegration is macroscopically visible, and according to the pharmacopoeia is tested employing a special apparatus, secondary disintegration is hardly perceptible or measurable, although it is a direct prerequisite of the dissolution of active ingredient. It follows that even if usual tablets are retained in the mouth until they are macroscopically disintegrated, this does not necessarily mean that they have already released the active substances contained therein, whereas flat, film- or paper-like active substance carriers are capable of doing so within a few seconds, up to minutes, after application thereof. Insofar, the latter are better suitable than tablets for introducing active substances

more quickly into the organism, and they can be advantageously used where a rapid onset of action is required or desirable, thus, for example, in the administration of analgesics, antiallergics, antitussives, antiemetics, active substances against angina pectoris, migraine, hypotension or hypotonia, etc.

Despite these obvious advantages, such flat administration forms have hitherto hardly been successful. Obviously, the advantage as compared to conventional administration forms does not suffice for many manufacturers of pharmaceutics to develop products of this type comprising the usual active ingredients and to pursue the legal drug approval thereof, which involves considerable effort and high costs. Moreover, existing production machinery and existing know-how cannot be used for these novel products; this means that the necessity of large investments would arise. Despite the above-described advantages of flat, film- or paper-like administration forms, the therapeutic and/or economic advantage over conventional tablets in administration of common active substances which are also perorally applicable is not great enough to justify the costs of switching over to these administration forms.

The present invention provides a pharmaceutical preparation for the treatment of off-phases of Parkinson's disease, said preparation being a mucoadhesive and foil-shaped, paper-shaped or wafer-shaped administration form for application in the oral cavity and release of active substance(s) to the oral mucosa, said preparation having a content of apomorphine or one of its pharmaceutically acceptable salts, characterized in that said mucoadhesive preparation disintegrates after application in the oral cavity and is based either - on a combination of polyvinyl pyrrolidone and starch, or - on a combination of polyvinyl alcohol, SiO_2 and glycerol.

The present invention also provides the use of a mucoadhesive pharmaceutical preparation having a content of apomorphine or one of its pharmaceutically acceptable salts in combination with at least one further active substance which suppresses or alleviates an unwanted side effect of apomorphine, for the treatment of Parkinson's disease, said preparation being a foiled-shaped, paper-shaped or wafer-shaped administration form for application in the oral cavity and release of active substance(s) to the oral mucosa which disintegrates after application in the oral cavity.

The present invention further provides the use of a mucoadhesive pharmaceutical preparation having a content of apomorphine or one of its pharmaceutically acceptable salts for the treatment of Parkinson's disease, said preparation being a foiled-shaped, paper-shaped or wafer-shaped administration form for application the oral cavity and release of active substance(s) to the oral mucosa which disintegrates after application in the oral cavity and which is multilayered, with only one layer having mucoadhesive properties.

In addition, the invention provides the use of a pharmaceutical preparation as described herein for the treatment of off-phases in Parkinson's disease.

As will be explained in the following, an administration form according to Claim 1 may be considered superior to a conventional oral administration form for administerting apomorphine – both from the economical as well as the therapeutical point of view; it is especially suitable for the therapy of Parkinson's disease.

Part of the symptoms and signs of Parkinson's disease is fluctuating dyskinesia, which is hardly accessible to pharmacotherapy and which is known under the term of "on-off phenomenon". This is the sudden change between good mobility and akinesia. The active agent apomorphine, a potent dopamine agonist, is suitable for acute therapy of the "off phases". However, for this purpose, apomorphine must be injected subcutaneously since it is hardly bioavailable after peroral administration, that is it appears in the blood circulation only to the very small extent of a few percent of the dose taken. Presumably, the reason for the lack in bioavailability lies in the extensive decomposition of the substance during the first liver passage following gastrointestinal absorption ("first-pass effect").

A possibility of avoiding the first-pass effect in oral administration is to bring the active substance to absorption already on the oral mucosa. In order to enter the central systemic circulation, an active substance which enters into the blood via the oral mucosa does not have to first pass the portal system and thus, in concentrated form, the liver, which metabolizes the active substance. A

prerequisite for buccal or sublingual application, however, is a sufficient permeability of the oral mucosa to the active substance, taking into consideration the required dose. Permeability in turn depends to a large extent on the physicochemical properties of the active substance. Buccal or sublingual administration of apomorphine appears to be very much desirable, due to the fact that injections of the patient are thereby avoided.

In recent years several research groups have therefore attempted to apply apomorphine via the oral mucosa. In fact, it has been possible to detect a relevant absolute bioavailability after sublingual administration in several experiments carried out independently from each other, as, for example, by Gancher et al. (Movement Disorders 6 [1991], pages 212-215), who found values of bioavailability between 10 and 22%. Montastruc et al. (Clin.Neuropharmacol. 14 [1991], pages 432 - 437) showed the equivalents of 30 mg of apomorphine sublingually, to 3 mg of the active substance subcutaneously. Similar results are found in Hughes et al. (Clin.Neuropharmacol. 14 [1991], pages 556-561), Durif et al. (Eur.J.Clin.Pharmacol.41 [1991], pages 493 - 494), and others.

It is to be criticized, however, that nowhere in the methodic portion of the publications of these studies have the parameters of the sublingual application themselves been defined. The only indications in this respect are made by Gancher et al., who instruct the test persons to keep the apomorphine tablets of 6 mg each under their tongue until they are dissolved. Where the tablets had not disintegrated after 5 minutes, the test persons were allowed to take a small drink of water, but not to swallow this. In the other applications it was obviously not ensured at all that either a portion of the active substance dose that was as great as possible or at least a

portion that came as near to being equally large as possible was available to the oral mucosa for absorption from the administration form. At least the duration of action, however, should be selected so as to be sufficient and constant, and swallowing of saliva should be eliminated over a constant period of time in order to methodically limit sublingual application against a peroral one. Moreover, the administration form administered in all of the above mentioned cases, namely a peroral tablet, is to be regarded, as has already been stated, as totally unsuitable for sublingual application. Presumably, it was precisely this problem which caused the high variability observed in the above mentioned studies.

This is completely different for the application of apomorphine by means of an administration form according to Claim 1. This administration form can be brought into direct contact with the oral mucosa. Due to the flat shape, immediately after application about half of the surface of the administration form, which is large any way, is located directly on the mucosa. The apomorphine released thus encounters two factors particularly favourable for entry into the body, namely a short diffusion path and a large diffusion area. This diminishes the portion of apomorphine that is swallowed, which in the case of other active agents would not be a particular problem. However, with apomorphine, swallowing of the active substance should be avoided if possible, or to be reduced since for the above mentioned reasons swallowed apomorphine is ineffective.

Even in the case of the most simple embodiment as a rapidly disintegrating administration form according to the invention, i.e. having a disintegration time of up to 15 min following application or following introduction into aqueous media, it emerged in the case of one test person

that an apomorphine-containing film is superior to an apomorphine-containing tablet.

An improved contact of the pharmaceutical preparation with the oral mucosa can be achieved through selecting the auxiliary substances. It is known of certain orally applicable auxiliary agents which are frequently used in pharmaceutics that they have mucoadhesive properties. Examples for such mucoadhesive substances are polyacrylic acid, carboxymethylcellulose, tragacanth, alginic acid, gelatin, hydroxymethylcellulose, methylcellulose and gum arabic. In addition, it is known of various non-mucoadhesive substances that in certain mixing ratios they also develop mucoadhesive properties. An example for such a mixture is glycerol monooleate/water in a ratio of 84:16 (Engström et al., Pharm. Tech. Eur. 7 [1995], No. 2, pages 14-17).

Where mucoadhesive auxiliary substances are used, it is preferable for the administration form of the pharmaceutical preparation according to the invention to have a two-layer or multi-layer structure, whereby only that layer which upon application is to come into contact with the mucosa should be equipped with mucoadhesive properties. This prevents the preparation from conglutinating various parts of the mucosa with each other, which would lead to sensations of considerable discomfort during application.

Good adhesion of the administration form leads to the active substance being optimally available for absorption. In addition, it is the prerequisite for a further, preferred embodiment of the invention, namely a controlled-release preparation. In the preparation according to the invention, the active substance amount, respectively the portion of the active substance dose administered, that is absorbed is dependent not only on the contact surface and

the permeability of the mucosa, but also on the duration of contact. In order to allow a larger amount of active ingredient to enter the body via the relatively small surface of the oral mucosa, it may be necessary to permit a long duration of contact; this, however requires that the preparation does not disintegrate too rapidly, but, through the addition of auxiliary substances that are slightly or slowly soluble in saliva, releases the active substance for the desired duration of time. Suitable auxiliary substances may be, for example, film-forming polymers having poor water-solubility, such as ethylcellulose, cellulose acetate, highly hydrolized polyvinyl alcohol and many more.

Administration of apomorphine typically results in unwanted side effects. In the first place, nausea, vomiting and decrease in blood pressure are to be mentioned. These side effects must be regarded as being serious and as imposing limits on therapy. However, it is known that through simultaneous administration of antiemetically effective dopamine antagonists such as metoclopramide, but especially domperidone, the occurrence of side effects can be eliminated or alleviated without the amorphine losing its anti-Parkinson action.
A further preferred embodiment of the present invention therefore contains as active substances apomorphine in combination with a dopamine antagonist in a combination.

In the following, preparation examples will be given of the pharmaceutical preparation according to the invention:

Example 1:

73.8 g	H_2O
5.5 g	TiO_2
18.4 g	polyvinyl pyrrolidone
18.4 g	potato starch
23.3 g	ethanol

4.0 g	H_2O
16.6 g	apomorphine HCI
1.8 g	aroma
1.2 g	sweetener
3.0 g	acidifying agent

H_2O is placed in a heatable, mixing vessel which can be evacuated. Polyvinylpyrrolidone is dispersed therein and allowed to swell. TiO_2 is dispersed in this mass. To accelerate the swelling process of the polivinyl-pyrrolidone, the mass may be heated. At room temperature, potato starch is dispersed in the homogeneous mass. Ethanol, residual H_2O and apomorphine HCI are added while stirring. The mass is heated to 100°C while stirring. After cooling to room temperature, aroma, sweetener and acidifying agent are added, and the mass is degasified under vacuum. The mass is spread onto a suitable carrier material using a doctor knife, and is dried for 30 minutes at 80°C. Dosage units are punched out with a wad punch.

Example 2:

135.8 g	H_2O
35.7 g	polyvinyl alcohol
9.9 g	TiO_2
46.5 g	SiO_2
20.0 g	glycerol (85%)
50.0 g	apomorphine HCI
4.8 g	aroma
3.2 g	sweetener
8.0 g	acidifying agent

H_2O is placed in a heatable mixing vessel which can be evacuated, and TiO_2 is dispersed therein. Polyvinyl alcohol and apomorphine HCI are powdered thereto, and are homogenized while heating to about 80°C. The mass is degasified under vacuum. After cooling to room temperature,

SiO_2, glycerol, aroma, sweetener and acidifying agent are added and homogenized. The mass is degasified under vacuum. The mass is spread onto a suitable carrier material using a doctor knife, and is dried for 30 minutes at 80°C. Dosage units are punched out with a wad punch.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

The claims defining the invention are as follows:

1. Pharmaceutical preparation for the treatment of off-phases of Parkinson's disease, said preparation being a mucoadhesive and foil-shaped, paper-shaped or wafer-shaped administration form for application in the oral cavity and release of active substance(s) to the oral mucosa, said preparation having a content of apomorphine or one of its pharmaceutically acceptable salts,
characterized in that said mucoadhesive preparation disintegrates after application in the oral cavity and is based either
- on a combination of polyvinyl pyrrolidone and starch, or
- on a combination of polyvinyl alcohol, SiO_2 and glycerol.

2. Pharmaceutical preparation according to claim 1, characterized in that it is multilayered, with only one layer having mucoadhesive properties.

3. Pharmaceutical preparation according to claim 1 or 2, characterized in that it contains at least one further active substance.

4. Pharmaceutical preparation according claim 3, characterized in that said at least one further active substance is a substance which suppresses or alleviates an unwanted side effect of apomorphine.

5. Pharmaceutical preparation according claim 4, characterized in that said further active substance is domperidone.

6. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that it is present separated into doses, and can be brought into direct contact with the oral mucosa.

7. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that it contains agents for the retarded release of active substance.

8. Pharmaceutical preparation according to claim 7 wherein said agents are film-forming polymers having poor water-solubility, preferentially selected from the group consisting of ethyl cellulose, cellulose acetate and highly hydrolyzed polyvinyl alcohol.

9. The use of a mucoadhesive pharmaceutical preparation having a content of apomorphine or one of its pharmaceutically acceptable salts in combination with at least one further active substance which suppresses or alleviates an unwanted side effect of apomorphine,
for the treatment of Parkinson's disease, said preparation being a foil-shaped, paper-shaped or wafer-shaped administration form for application in the oral cavity and release of active substance(s) to the oral mucosa which disintegrates after application in the oral cavity.

10. The use of a mucoadhesive pharmaceutical preparation having a content of apomorphine or one of its pharmaceutically acceptable salts for the treatment of Parkinson's disease, said preparation being a foil-shaped, paper-shaped or wafer-shaped administration form for application in the oral cavity and release of active substance(s) to the oral mucosa which disintegrates after application in the oral cavity and which is multilayered, with only one layer having mucoadhesive properties.

11. The use of a mucoadhesive pharmaceutical preparation according to claim 10 wherein said preparation contains at least one further active substance which suppresses or alleviates an unwanted side effect of apomorphine.

12. The use of a mucoadhesive pharmaceutical preparation according to claim 9 or 11 wherein said further active substance is domperidone.

13. The use of a pharmaceutical preparation according to any one of claims 9 to 12, wherein said preparation contains agents for the retarded release of active substance.

14. The use of a pharmaceutical preparation according to claim 13, wherein said agents are film-forming polymers having poor water-solubility, preferentially selected from the group consisting of ethyl cellulose, cellulose acetate and highly hydrolyzed polyvinyl alcohol.

15. The use of a pharmaceutical preparation according to any one of claims 1 to 8 for the treatment of Parkinson's disease.

16. Use of apomorphine for the preparation of a pharmaceutical preparation according to anyone of claims 1-8 for the treatment of Parkinson's disease.

17. A pharmaceutical preparation or use thereof substantially as herein described with reference to the examples.

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